TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER: P67254US0

US APPLICATION NO. (If known, see 37 CFR 1.5): 09/926444

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/04003	4 May 2000	4 May 1999

TITLE OF INVENTION

LABORATORY TEST OF A BODY FLUID OR TISSUE SAMPLE

APPLICANT(S) FOR DO/EO/US

Wilhelm HOERRMANN

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☒ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
    International Search Report - EPO
    First Page of Publication
    International Preliminary Examination Report - with no annexes

US APPLICATION NO.(If known, see 37 CFR 1 5)	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/926444	PCT/EP00/04003	P67254US0

	CALCULATIONS	PTO USE ONLY
17. ☒ The following fees are submitted:		
Basic National Fee (37 CFR 1.492(a)(1)-(5)):		
Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) .. $710.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .. $740.00		
Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$1040.00**		
International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) $100.00		
Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) **$890.00**		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$ 890.00	
Surcharge of $130.00 for furnishing the **oath or declaration** later than ☐ **20** ☒ **30** months from the earliest claimed priority date (37 CFR 1.492(e)).	$ 130.00	

Claims	**Number Filed**	**Number Extra**	Rate		
Total Claims	**19** - 20 =	-0-	x $18.00	$	
Independent Claims	**1** - 3 =	-0-	x $84.00	$	
Multiple Dependent Claim(s) (if applicable)			+ $280.00	$	
TOTAL OF ABOVE CALCULATIONS =				$ 1020.00	
Reduction by 1/2 for filing by **small entity**, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				$	
SUBTOTAL =				$ 1020.00	
Processing fee of $130 for furnishing the **English translation** later than ☐ **20** ☐ **30** months from the earliest claimed priority date (37 CFR 1.492(f))				$	
TOTAL NATIONAL FEE =				$ 1020.00	
Fee of $40.00 for recording the enclosed **assignment** (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				$	
TOTAL FEES ENCLOSED =				$ 1020.00	
				Amt. to be refunded:	$
				Amt. charged:	$

a. ☒ A check in the amount of $ 1020.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. **06-1358** in the amount of $ ____ to cover the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. **06-1358**. A duplicate copy of this sheet is enclosed.

SEND ALL CORRESPONDENCE TO:

JACOBSON HOLMAN PLLC
400 7th Street, N.W., Suite 600
Washington, DC 20004
202-638-6666
CUSTOMER NUMBER: 00136

By Harvey B. Jacobson, Jr.
Harvey B. Jacobson, Jr.
Reg. No. 20,851

JPH&S 3/95

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: Wilhelm HOERRMANN

Serial No.: New

Filing Date: November 5, 2001

For: LABORATORY TEST OF A BODY FLUID OR TISSUE SAMPLE

PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE SPECIFICATION

On page 1, immediately following the title, please insert the following sentence: --This is a nationalization of PCT/EP00/04003 filed May 4, 2000 and published in German.--

Please replace the paragraph on page 5, line 12 through line 19 with the following rewritten paragraph:

--Preferably the sample to be analyzed is prepared in several steps. An internal standard (s.o) is added to the body fluid and/or the tissue; the mixture, obtained according to this step, is hydrolized. Then at least one alkali hydroxide and at least one alkali carbonate are added to the hydrolyzed mixture. The product from this step is treated with a reagent eliminating the disturbing substance, and finally the cis-4-hydroxyproline and its derivative content is analyzed quantitatively. In this respect, it has proved advantageous that the hydrolysis in the presence of a strong mineral acid, in particular hydrochloric acid, occurs at a raised temperature, *preferably between 80 degrees C and 120 degrees C*, in particular preferably at a temperature of approximately 100 degrees C. Similarly it is especially--

Applicant: Wilhelm HOERRMANN

REMARKS

The foregoing Preliminary Amendment is requested in order to place the application in better form for examination.

Early action on the merits is respectfully requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By _____
Harvey B. Jacobson, Jr
Reg. No. 20,851

400 Seventh Street, N.W.
Washington, D.C. 20004-2201
(202) 638-6666

Atty. Docket: P67254US0
Date: November 5, 2001
HBJ/cmf

Laboratory Test of a Body Fluid or Tissue Sample

Medicine knows the term "predisposition for a disease", which means that some people have a higher probability of acquiring a specific disease than others. If the result of such a predisposition, which is often genetically induced, is a disease that does not produce clinical symptoms, then it is often the case that the corresponding disease cannot be detected at all or only with very expensive and stressful methods.

So that the execution of such expensive and stressful methods can be limited to cases exhibiting a high probability for the presence of a predisposition for a disease, it would be desirable to find an indicator for a predisposition for a disease at a low cost for the purpose of testing in the laboratory a body fluid or tissue sample.

The present invention solves this problem by detecting cis-hydroxyproline and derivatives thereof by means of quantitative analysis in a laboratory test of a body fluid or tissue sample. The present invention uses the knowledge that cis-hydroxyproline, in particular cis-4-hydroxyproline, is an endogenic substance, whose occurrence in the body in the body fluids and in the tissue depends on the predisposition for different

diseases. This knowledge is quite surprising. Not only because to date such a dependency was not known, but also because to date it was not even known that cis-hydroxyproline is, indeed, an endogenic substance. Rather the experts assumed in the past that the body does not synthesize cis-hydroxyproline, in particular cis-4-hydroxyproline. It was only known that trans-4-hydroxyproline is formed in the human body.

The importance of the value of a laboratory test of a body fluid or tissue sample for this trans form of hydroxyproline has already been known for a long time. Hence, bone destruction, especially in the case of osteoporosis, can be confirmed and measured in detail by means of quantitative analysis.

The present invention proceeds from the recognition that the cis form of hydroxyproline, which had not been regarded to date as an endogenic substance, is a significant factor in other diseases, including in particular cancer and cardiovascular diseases.

The quantitative analysis of cis-hydroxyproline that is performed according to the present invention has proved to be not only expedient for finding an indicator for a predisposition for a disease, but also the invention can be used for a disease that already exists clinically. The quantitative analysis of cis-4-hydroxyproline in the body fluid and / or tissues can show in particular a low level of this substance, which in the prestage or early manifestation of diseases can relate to an inadequate endogenic synthesis of this substance

due to metabolic causes. Similarly the use of the present invention can detect values that are higher than the normal cis-4-hydroxyproline values and which can relate to a change in the tissue or even necrosis.

Especially important is also the determination of cis-hydroxyproline, according to the invention, for the purpose of following the course of development of the disease, a feature that is also important for the evaluation of the efficacy of the therapeutic measures and their dosing.

Therefore, the present invention comprises the detection and quantitative analysis of cis-hydroxyproline in organisms of humans and mammals, and in particular in all body fluids, like blood, urine, lymph, cerebrospinal fluid, ascites, other exudates, but also in the body tissues.

The analysis relates not only to cis-4-hydroxy-L-proline, but also to other configurations of cis-hydroxyproline, like the L and D form and a different ring positioning of the hydroxyl group. It also relates to derivatives of cis-hydroxyproline, like N-methyl-cis-hydroxyproline, and it relates to those peptide and other compounds, from which the said substances have to be eluted first for the purpose of testing.

The said compound can be determined with various known analytic methods, which include gas chromatography, column chromatography, mass spectroscopy,

HPLC [= high performance liquid chromatography] method, ion exchange chromatography, immunoassay, radio immunoassay, enzyme immunoassay, fluorescence immunoassay and others. In the case of cleavage of peptide and similar compounds, the use of conventional conservative methods must be considered.

A preferred method, which can be used within the scope of the present invention to determine cis-hydroxyproline and its derivatives in a body fluid or tissue sample, is disclosed in claim 4. Preferred further developments can be inferred from the dependent claims referring to claim 4.

According to the method, disclosed in claim 4, to determine cis-hydroxyproline and its derivatives in the body fluids and / or tissues, the sample to be analyzed is prepared to eliminate disturbing substances; and the cis-hydroxyproline and its derivative content is determined quantitatively in this sample. The definition of the term "disturbing substance" is based on the analysis method that is used. Should the HPLC method be used, the disturbing substances are those that can falsify the measurement of cis-hydroxyproline and its derivatives based on a corresponding absorptivity at essentially the same retention time. Such substances must be eliminated. Hence, it is possible to determine cis-4-hydroxyproline, for example, in a concentration of < 1 μg / ml that is present in the human body.

Especially preferred is the determination of the cis-hydroxyproline content in the body fluids and / or tissues by means of comparison with an external and / or internal standard. Thus, it is possible to quantify reliably the concentration of cis-hydroxyproline, even in the aforementioned small concentrations.

To determine the cis-4-hydroxyproline content using the HPLC method at an excitation wavelength of 471 nm, cis-3-hydroxyproline (cis-3-HYP) has proved to be a suitable internal standard. Using a suitable separating column (for example, RP 8) and an optimal measuring temperature (for example, 60 degrees C), its retention time (6.00 min.) is longer than that of cis-4-hydroxyproline (4.60 min.) and trans-4-hydroxyproline (3.30 min.).

Preferably the sample to be analyzed is prepared in several steps. An internal standard (s.o) is added to the body fluid and / or the tissue; the mixture, obtained according to this step, is hydrolized. Then at least one alkali hydroxide and at least one alkali carbonate are added to the hydrolyzed mixture. The product from this step is treated with a reagent eliminating the disturbing substance; and finally the cis-4-hydroxyproline and its derivative content is analyzed quantitatively. In this respect, it has proved to be advantageous that the hydrolysis in the presence of a strong mineral acid, in particular hydrochloric acid, occurs at a raised temperature, in particular preferably at a temperature of approximately 100 degrees C. Similarly it is especially

advantageous, if the pH of the hydrolized mixture is adjusted to a value ranging from 8.5 to 9.0. Hydroxides, carbonates and / or biscarbonates of sodium or potassium can be used preferably as the basic alkali metal compounds that are appropriate for the invention.

In particular, compounds, containing keto groups, are suitable as the reagent, with which the disturbing substances are removed. In this respect, aldehydes, in particular ortho phthaldialdehyde at a concentration ranging from 45 to 55 g/l, in particular at a concentration of 50 g/l, have proved to be suitable as the keto compounds. After the solution has been allowed to stand at room temperature, any precipitate that might have formed is removed by separation by means of sedimentation, centrifugation, filtration or another suitable method.

Then an aqueous phosphate buffer and a derivatization reagent, with which the cis-4-hydroxyproline to be determined is chemically modified, are added as the mobile solvent to the solution, which is obtained above and is freed of any precipitate. Typical derivatization reagents, which are also known in the state of the art, are azo dyes, whereby dabsyl chloride at a concentration ranging from 220 to 270 mg/l, in particular at a concentration of 242.8 mg/l, is especially interesting. To accelerate the reaction, the mixture comprising the sample to be analyzed, the buffer and the derivatization reagent is heated in an advantageous manner for a short period (for example, 15 minutes) to temperatures of approximately 70 degrees C.

If necessary, the reaction solution, obtained in the preceding step, is cooled down to room temperature and optionally a small quantity of the same aqueous phosphate buffer that was added in the preceding step is added as the mobile

solvent. Then the quantitative analysis of cis-4-hydroxyproline and its derivatives is carried out with a sample, which is prepared in such a manner, by means of HPLC.

The invention is explained in detail below with the aid of the examples.

Example 1:

Preparation of external / internal standard solutions to quantify cis-4-hydroxyproline in body fluids

a) Preparation of an external standard solution: cis-4-(L)-HYP, trans-4- (L) -HYP, cis-3- (DL) - HYP

1) Stock solution: c = 0.1 mg/ml; (identical volumes of a solution of 5 mg cis-4-HYP and 5 mg trans-4-HYP in 25 ml superpure water (bidistilled water) and a solution of 5 mg cis-3-HYP in 25 ml superpure water are mixed)

2) mix 1 ml HCl (6 M) and 1 ml of 1)

3) mix 1 ml of 2) with 5 ml NaOH (0.5 M) and 5 ml Na_2CO_3 (0.25 M)

4) adjust pH value to 8.5 by adding HCl (32%, 10 M)

5) mix 10 ml of 4) with 15 ml dabsyl chloride (c = 242.8 mg/l), heat to 70 degrees C for 10 minutes

6) allow to cool to room temperature, then fill up to 25 ml with acetone (should turbidity develop, a couple of drops of superpure water are added until dissolution)

7) 25 ml of 6) are filled up to 146.156 ml with superpure water.

b) Preparation of an internal standard solution (IS): cis-3-(DL)-HYP
Identical parts by volume of the solution of cis-3-HYP (5 mg in 25 ml superpure water), used above, and superpure water are mixed.

Example 2:

Quantitative analysis of cis-4-HYP in urine:

1) 1 ml HCl (10 M) and 0.1 ml IS, according to example 1, are added to 1 ml urine to be analyzed and hydrolyzed at 100 degrees C for 16 hours.

2) 0.25 ml of an aqueous solution of NaOH (16 M) and Na_2CO_3 (4 M) respectively are added to 1 ml of 1). Optionally the pH value is adjusted with 10 M HCl to a pH ranging from 8.5 to 9.0.

3) 0.5 ml of 2) is mixed intimately with 0.2 ml ortho-phthaldialdehyde (c = 50 g/l) and with 0.2 ml superpure water and allowed to stand for 60 minutes. Then any precipitate that may have accumulated is centrifuged off.

4) 0.2 ml of an aqueous phosphate buffer (22 % by weight acetone nitrile, 78 % by weight superpure water, di-sodium

hydrogen phosphate dodecahydrate, citric acid, pH = 4.7) and 0.2 ml dabsyl chloride (c = 242.8 mg/l) are added to 0.15 ml of the supernatent solution of 3); the reaction vessel is tightly closed and heated to 70 degrees C for 15 minutes in the oven.

5) The reaction solution of 4) is cooled to room temperature, and then another 0.3 ml aqueous phosphate buffer is added as the mobile solvent.

6) HPLC measurement using an RP 8 separating column at a measurement temperature of 60 degrees C in the column oven and an excitation wavelength of 471 nm: injection volume: 20 μl

Urine samples of 10 male and 10 female subjects of different ages were tested.

The following table lists the measurement results and the urea, creatinine and total protein data of the respective sample.

Table 1: Chromatographic Quantification of cis-4-HYP of Native Urines.

X[a]	Age (Y), Sex	Urea (mg/dl)	Creatinine (mg/dl)	U/CSF (mg/dl)	c(trans-4-HYP) (μg/ml)	c(cis-4-HYP) (μg/ml)
51	62, f	675 T	34.41	< 2	6.7	0.4
52	56, f	1628	71.42	3.1	8.6	0.4
53	19, f	1360	141.81	15.1	38.0	1.3
54	6 days, f	130 T	12.90	7.6	110	1.8
55	49, f	410 T	13.13	10.4	6.8	0.2
56	86, f	474 T	23.40	< 2	4.9	0.3
57	56, f	1726	105.35	9.4	24	1.2
58	83, f	763 T	48.03	5.5	5.8	0.5
59	33, f	802 T	80.23	2.6	22.8	0.3
60	65, f	957	16.34	< 2	12.6	0.2
I[b]					8.4	0.6
II[b]					9.4	1.4
III[b]					8.9	11.6
61	35, m	1866	151.27	4.6	26.9	0.5
62	69, m	2480	51.57	5.3	22.6	0.9
63	81, m	2197	91.77	4.8	45.0	1.5
64	86, m	2068	130.50	7.8	24.5	1.7
65	50, m	2221	194.16	9.1	31.2	0.9
66	60, m	772 T	120.69	5.4	20.3	0.8
67	57, m	2597	171.67	13.4 H	25	0.7
68	45, m	1375	70.94	< 2	7.6	0.5
69	35, m	351 T	74.06	12.5 H	17	0.2
70	69, m	337 T	75.23	6.8	5.9	0.2
I[b]					8.6	0.3
II[b]					7.9	4.5
III[b]					8.6	11.1

a) sample - number - EOXO - X

b) control urine I - III

I: c(cis-4-HYP) = 0.3 μg/ml

II: c(cis-4-HYP) = 1.4 μg/ml

III: c(cis-4-HYP) = 11.2 μg/ml

I - III: c(trans-4-HYP) = 8.7 μg/ml

Claims

1. Laboratory test of a body fluid or tissue sample,
characterized in
that cis-hydroxyproline and derivatives thereof are detected by means of quantitative analysis.

2. Laboratory test of a body fluid or tissue sample, as claimed in claim 1,
characterized in
that cis-4-hydroxyproline is detected by means of quantitative analysis.

3. Laboratory test of a body fluid or tissue sample, as claimed in claim 1,
characterized in
that the quantitatively analytic detection of cis-hydroxyproline and its derivatives is carried out by means of HPLC, column chromatography, gas chromatography, mass spectroscopy, ion exchange chromatography, immunoassay, radio immunoassay, enzyme immunoassay, fluorescence immunoassay or other corresponding antibody methods.

4. Process for determining cis-hydroxyproline and its derivatives for the purpose of a laboratory test of a body fluid or tissue sample, as claimed in claim 1,
characterized in
that the body fluid or tissue sample to be analyzed is prepared to eliminate disturbing substances; and that the cis-hydroxyproline and its derivative content is determined quantitatively in this sample.

5. Process, as claimed in claim 4,
characterized in
that the determination of cis-hydroxyproline and its derivatives is performed by means of HPLC, gas chromatography, column chromatography, mass spectroscopy, ion exchange chromatography, RIA, ELISA or fluorescence immunoassay.

6. Process, as claimed in claim 4,
characterized in
that the cis-hydroxyproline and its derivative content is determined by means of comparison with an external and / or internal standard.

7. Process, as claimed in claim 4, wherein the cis-4-hydroxyproline content in the body fluid and tissue sample is determined by means of HPLC, comprising the following steps:
   a) An internal standard is added to the body fluid and / or the tissue sample.
   b) The mixture, obtained according to step a), is hydrolized.
   c) At least one alkali hydroxide and at least one alkali carbonate are added to the product, obtained according to step b).
   d) A reagent eliminating the disturbing substance and a derivatization reagent are added to the product, obtained from step c); and
   e) the cis-4-hydroxyproline and its derivative content is determined in the product obtained in step d).

8. Process, as claimed in claim 7,
characterized in
that before step b) an acid is added.

9. Process, as claimed in claim 8,
characterized in
that hydrolysis takes place in the presence of hydrochloric acid at a temperature ranging from 80 degrees C to 120 degrees C.

10. Process, as claimed in claim 7,
characterized in
that the alkali metal compounds added in step c) are hydroxides or carbonates of sodium or potassium.

11. Process, as claimed in claim 7,
characterized in
that the pH value in step c) is adjusted to a pH ranging from 8.5 to 9 with the addition of HCl.

12. Process, as claimed in claim 7,
characterized in
that in step d) ortho-phthaldialdehyde (OPA) and as the derivatization reagent an azo dye are added.

13. Process, as claimed in claim 7,
characterized in
that prior to the quantitative analysis of cis-4-hydroxyproline and its derivatives in step e) the temperature is lowered.

14. Process, as claimed in claim 4,
characterized in

that the body fluid sample is a urine sample or a blood sample.

15. Process, as claimed in claim 7,
characterized in
that cis-3-hydroxyproline is used as the internal standard (IS).

16. Analysis kit to carry out the process, as claimed in claim 7, comprising HCl (10 M), NaOH (16 M), Na_2CO_3 (4 M), ortho-phthaldialdehyde, aqueous phosphate buffer and dabsyl chloride.

17. Analysis kit, as claimed in claim 16,
characterized in
that the concentration of ortho-phthalaldehyde ranges from 45 to 55 g/l.

18. Analysis kit, as claimed in claim 16,
characterized in
that the concentration of dabsyl chloride ranges from 220 to 270 mg/l.

19. Analysis kit, as claimed in claim 16,
characterized in
that it includes at least one RP 8 separating column.

DECLARATION AND POWER OF ATTORNEY U.S.A.

ALL PATENTS, INCLUDING DESIGN
FOR APPLICATION BASED ON PCT, PARIS CONVENTION;
NON PRIORITY; OR PROVISIONAL APPLICATIONS

FOR ATTORNEYS' USE ONLY
ATTORNEYS' DOCKET NO.
P67254US0

101 102

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original, first and sole inventor (if only one name is listed at 201 below), or an original, first and joint inventor (if plural inventors are named below at 201-203, or on additional sheets attached hereto) of the subject matter which is claimed and for which patent is sought on the invention entitled

LABORATORY TEST OF A BODY FLUID OR TISSUE SAMPLE

which is described and claimed in.

[X] PCT International Application No. **PCT/EP00/04003** filed **May 4, 2000**

[ ] the attached specification

[ ] the specification in application Serial No. _____ filed _____

(if applicable) and amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above
I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1 56
I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed·

Prior Foreign Application(s)

(Number)	(Country)	(Day/Month/Year Filed)	Priority Claimed Yes	No
199 20 434.9	**GERMANY**	**4 May 1999**	[X]	[ ]
			[ ]	[ ]
			[ ]	[ ]

103 104

I hereby claim the benefit under Title 35, United States Code,§119(e) of any United States provisional application(s) listed below.

Application No _____ Filing Date _____ Application No _____ Filing Date _____

105

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No)	(Filing Date)	(Status: patented, pending, abandoned)

POWER OF ATTORNEY· As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith HARVEY B JACOBSON, JR. (20,851); JOHN CLARKE HOLMAN (22,769); MARVIN R. STERN (20,640); ALLEN S MELSER (27,215); MICHAEL R. SLOBASKY (26,421); JONATHAN L. SCHERER (29,851); IRWIN M AISENBERG (19,007); WILLIAM E. PLAYER (31,409); YOON S. HAM (45,307) and NATHANIEL A. HUMPHRIES (22,772)

SEND CORRESPONDENCE TO·	DIRECT TELEPHONE CALLS TO.
CUSTOMER NO. 00136 or **JACOBSON HOLMAN** **PROFESSIONAL LIMITED LIABILITY COMPANY** **400 SEVENTH STREET, N.W.** **WASHINGTON, D.C. 20004**	(please use Attorney's Docket No) (202) 638-6666 **JACOBSON HOLMAN** **PROFESSIONAL LIMITED LIABILITY COMPANY**

*Inventor(s) name must include at least one unabbreviated first or middle name.

201 FULL NAME * OF INVENTOR	FAMILY NAME **HOERRMANN**	GIVEN NAME **Wilhelm**		MIDDLE NAME	
RESIDENCE & CITIZENSHIP	CITY **Iffeldorf**	STATE OR FOREIGN COUNTRY **GERMANY** DEX		COUNTRY OF CITIZENSHIP **GERMANY**	
POST OFFICE ADDRESS	POST OFFICE ADDRESS **Staltacher Str. 34**	CITY **Iffeldorf**	STATE OR COUNTRY **GERMANY**		ZIP CODE **D-82393**
202 FULL NAME * OF INVENTOR	FAMILY NAME	GIVEN NAME		MIDDLE NAME	
RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY		COUNTRY OF CITIZENSHIP	
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY		ZIP CODE
203 FULL NAME * OF INVENTOR	FAMILY NAME	GIVEN NAME		MIDDLE NAME	
RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY		COUNTRY OF CITIZENSHIP	
POST OFFICE ADDRESS	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY		ZIP CODE

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true, and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code; and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
DATE 15. NOV 2001	DATE	DATE

[ ] Additional inventors are named on separately numbered sheets attached hereto.